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Monkeypox Virus Beyond Endemic Regions: Insights into Genomic Evolution, Host–Virus Interactions, and Global Public Health Challenges

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Abstract

The monkeypox virus (MPXV), which is responsible for the zoonotic illness mpox, has traditionally been confined to the tropical forest regions of Central and West Africa. However, in recent years, the virus has expanded beyond its endemic range and has led to outbreaks across numerous countries worldwide. In this review, we examine how monkeypox virus interacts with its host, influencing infection processes, signalling pathways, disease progression, and immune responses. We also emphasize the evolving understanding of MPXV pathophysiology and epidemiology, while outlining the latest developments in strategies for prevention and therapeutic management of mpox. Adopting a One Health framework offers a promising strategy to curb ongoing mpox outbreaks and reduce the risk of future epidemics.

Keywords: Mpox; zoonotic illness; genomic organization; epidemiology; pathophysiology; ecological niche.

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1.0 Introduction

The monkeypox virus (MPXV or Mpox) belongs to the *Poxviridae* family and is classified under the *Orthopoxvirus* (OPV) genus(https://www.who.int/news-room/fact_sheets/detail/mpox). This genus also includes other human-pathogenic viruses such as variola virus (VARV, the causative agent of smallpox), vaccinia virus (VACV), camelpox virus (CMPV), and cowpox virus (CPXV) (Faye et al., 2018). MPXV is a double-stranded DNA (dsDNA) virus with brick-shaped virions measuring about 200–250 nm, which can be visualized under electron microscopy at approximately ×10,000 magnification (Karagoz et al., 2023). Phylogenetic studies divide MPXV into two clades: the West African (WA, Clade II) clade and the Congo Basin (CB, Clade I) clade. The latter, also known as the Central African (CA) clade, is associated with more severe clinical outcomes (Parikh et al., 2023; Masirika et al., 2024). MPXV was first identified in 1958 during outbreaks among laboratory monkeys in Copenhagen, Denmark (https://www.cdc.gov/monkeypox/about/index.html).

The first confirmed human case occurred in 1970 in the Democratic Republic of Congo (DRC) in a 9-month-old infant initially suspected to have smallpox (Halder et al., 2025). Amid the ongoing COVID-19 pandemic, the year 2022 witnessed the resurgence of another viral threat—monkeypox. This zoonotic disease, long endemic in parts of Africa, had occasionally produced sporadic but noteworthy cases outside the continent. Recognizing its rapid expansion, the World Health Organization (WHO) declared mpox a Public Health Emergency of International Concern (PHEIC) on June 23, 2022 (https://www.who.int/groups/monkeypox-ihr-emergency-committee). In recent years, the number of monkeypox cases has risen markedly, posing a major global health challenge. The re-emergence of the disease has been particularly concerning in immunocompromised individuals, where it has presented with severe dermatologic, respiratory, and neurological complications (Moghib et al., 2025). Addressing this threat requires improved understanding and re-evaluation of the virus.

The global outbreak of monkeypox virus (MPXV) has highlighted its potential to threaten international public health, particularly with the emergence of novel branches and lineages that complicate epidemic control and prevention strategies (Girometti et al., 2025). Whole-genome sequencing serves as a critical approach in this context, as it enables the identification of mutations that may enhance viral transmissibility or pathogenicity, providing crucial insights for real-time monitoring of global transmission patterns (Baden et al., 2024). This review provides an overview of current knowledge on MPXV, covering its epidemiology, possible animal reservoirs, transmission patterns, genomic evolution, infection biology, clinical features, diagnostic tools, available treatments, and preventive measures.

2.0 Epidemiology

The first human case of monkeypox was identified in the Democratic Republic of Congo (DRC) in 1970 (Mukadi-Bamuleka et al., 2025). Between 1970 and 1990, over 400 cases were reported across Africa, with the majority originating in the DRC (Zahmatyar et al., 2023). Additional cases during this period included six in the Central African Republic, two in Cameroon, three in Nigeria, two in Ivory Coast, four in Liberia, and single cases in both Sierra Leone and Gabon. In 1990, Cameroon documented four suspected cases of monkeypox, of which one was laboratory confirmed (Heymann et al., 1998). In 1996, the DRC experienced a large and prolonged outbreak of human monkeypox. The first confirmed case was recorded in February, and by August of the same year, 71 suspected infections had been reported (Mwanbal et al., 1997). By 1999, the number of documented cases in the country had exceeded 500. Between February and August 2001, 16 additional cases were identified in Equateur Province, DRC. Furthermore, a study by Anne et al conducted from 2001 to 2004 analysed vesicular fluid and scab samples from 136 suspected cases, confirming monkeypox in 51 individuals (Rimoin et al., 2007). The outbreak was linked to pets that became infected after close contact with imported small mammals from Ghana, including African rodents such as rope squirrels, tree squirrels, Gambian giant rats, brushtail porcupines, dormice, and striped mice. Laboratory investigations by the U.S. Centers for Disease Control and Prevention (CDC) confirmed infection in several of these animals through virus isolation and polymerase chain reaction (PCR) testing (Sale et al., 2006). Notably, no fatalities were reported, and human-to-human transmission did not occur, indicating a limited outbreak caused by the West African clade of MPXV (Huang et al., 2022). The 2022 global outbreak of monkeypox resulted in thousands of infections worldwide, following years of sporadic cases outside Africa, including those in the United Kingdom, Singapore, Israel, and the United States (Thornhill et al., 2022). In May 2022, multiple cases were detected in the United Kingdom. The first case was identified on May 6 in an individual with recent travel history to Nigeria, followed by two additional unlinked cases in London on May 12 (World Health Organization (16 May 2022). Disease Outbreak News). Within the following week, four more unrelated cases were documented. Table 1 below gives a summary of major human monkeypox outbreaks from 1970 to 2025.

PCR analysis confirmed that the outbreak was caused by the West African clade (Clade II) of MPXV, which is associated with milder disease outcomes compared to the Congo Basin clade (Clade I), with an estimated case-fatality rate of about 1% (Bogacka et al., 2025). The unusual progression of the 2022 outbreak prompted the World Health Organization (WHO) to classify monkeypox as an “evolving threat of moderate public health concern” on June 23, 2022, followed by its declaration as a “Public Health Emergency of International Concern” (PHEIC) on July 23, 2022 (Wenham & Eccleston-Turner, 2022). According to WHO’s recent multi-country external situation report,

published in February 2026, the global mpox situation remains moderately concerning, with sustained multi-country transmission across all WHO regions (Situation Report, PAHO/WHO, 2025). Between January 2025 and January 2026, over 54,800 confirmed cases and 221 deaths were reported across 98 countries, with Africa contributing the majority of recent cases (WHO, 2026). Post-2022 mpox epidemiology is characterized by a transition from a Clade IIb–dominated global outbreak to multi-clade circulation, with emerging Clade Ib and recombinant Ib/IIb strains driving ongoing transmission and geographic spread (Ortiz et al., 2025).

Table 1. Summary of major human monkeypox outbreaks from 1970 to 2025, highlighting case counts, geographic spread, and key events

Period/Outbreak	Location(s)	Key Statistics/Details	Clade/Notes
1970–1990	Africa (mainly DRC)	>400 cases in DRC; others: CAR (6), Cameroon (2+4 suspected/1 conf.), Nigeria (3), Ivory Coast (2), Liberia (4), Sierra Leone (1), Gabon (1)	Endemic in Central/West Africa
1996 (Feb–Aug)	DRC	71 suspected cases	Large, prolonged outbreak
By 1999	DRC	>500 documented cases	-
Feb–Aug 2001	Equateur Province, DRC	16 cases	-
2001–2004 (U.S. study)	USA (prairie dogs/pets)	136 suspected; 51 lab-confirmed; linked to imported Ghanaian rodents (squirrels, rats, porcupines, etc.); no human-to-human spread; no deaths	West African (Clade II); CDC-confirmed via PCR/virus isolation
May 2022 (initial)	UK (London)	1st case (May 6, Nigeria travel); +2 unlinked (May 12); +4 unrelated (next week)	Clade II (~1% case-fatality rate)
2022 Global (by Sep 13)	>100 countries	57,995 lab-confirmed cases; 18 deaths (9 countries)	Clade IIb (predominantly West African lineage)
Recent outbreaks (Jan 2025 – Jan 2026)	in Africa and reported from France, Portugal, Spain	Total confirmed cases : 54,817; with total deaths: 221 (98 countries)	Clade Ib
First-time mpox cases	Comoros, La Réunion		Clade Ib
	India and the United Kingdom		Recombinant strain (Clade Ib/IIb)

The 2022 global outbreak was predominantly caused by Clade IIb (West African lineage), which continues to circulate at low levels globally. In the current (2025–2026) phase, there is co-circulation of multiple clades, with increasing epidemiological importance of Clade I, especially Ib. (Mpox: Multi-country external situation report no. 63, WHO; 2026)

3.0 Mechanisms of viral infection

The Monkeypox virus (MPXV), a double-stranded DNA member of the *Orthopoxvirus* genus in the *Poxviridae* family, shares key infection features with the smallpox-causing Variola virus (Karagoz et al., 2023). Initial infection starts with the virus binding to host cell surfaces via interactions between its envelope proteins and receptors like heparan sulfate glycosaminoglycans. MPXV circulates in two main infectious forms: mature virions (MVs) that drive transmission between hosts, and enveloped virions (EVs) that promote spread from cell to cell inside the host (Hajjo et al., 2025). Entry into the cell happens primarily through macropinocytosis or fusion with the plasma membrane, releasing the viral core into the cytoplasm (Figure 1). There, the virus's packaged DNA-dependent RNA polymerase transcribes early genes, since all replication occurs outside the nucleus. These early gene products drive core uncoating, dampen host immunity,

and set the stage for DNA synthesis. Viral genome replication then unfolds in dedicated cytoplasmic structures called factories, employing a rolling-hairpin strategy to generate progeny DNA. Intermediate genes activate next, paving the way for late genes that produce structural components. New DNA combines with these proteins to form immature virions (IVs), which mature into MVs; a subset gains extra envelopes from Golgi or endosomal membranes to become EVs. MVs escape via cell lysis, while EVs bud out through exocytosis or actin-based propulsion, allowing covert dissemination without rapid host cell death (Figure 1) (Deng et al., 2025).

MPXV bolsters its survival by deploying immune countermeasures, including proteins that disrupt interferon signaling, neutralize cytokines, and halt apoptosis—delaying full immune activation and supporting extended replication. Together, these steps—binding, penetration, replication, morphogenesis, egress, and evasion—form a sophisticated cytoplasmic lifecycle optimized for MPXV persistence, spread, and virulence across hosts.

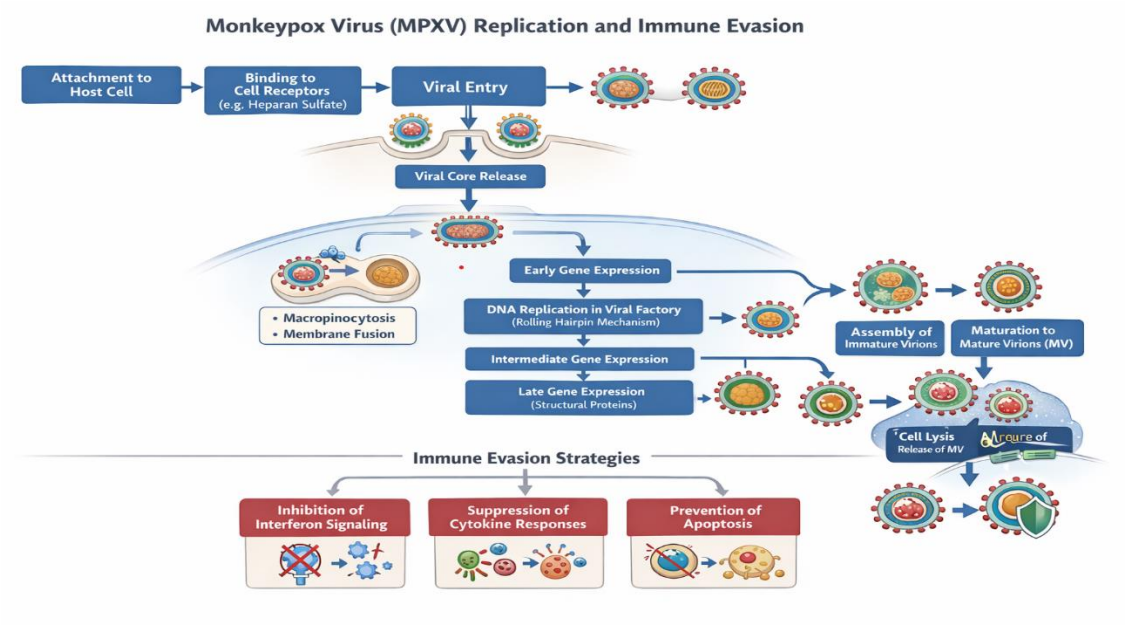

Figure 1: Schematic overview of the immune evasion mechanisms of Monkeypox virus (MPXV). *(Image created through Biorender)*

4.0 Monkeypox virus mutations:

Monkeypox virus (MPXV), a double-stranded DNA pathogen that targets both humans and animals, resides in the Orthopoxvirus genus of the Poxviridae family. Poxviruses stand out among animal viruses for their exceptionally large and intricate DNA genomes. The MPXV particle features four core elements: a central nucleocapsid housing the genome plus stabilizing proteins and fibrils, paired lateral bodies, a surrounding membrane, and an outermost lipoprotein envelope. Spanning about 197 kilobases, the MPXV genome has a conserved central segment of roughly 101 kb packed with genes for critical functions like replication, transcription, virion assembly, and egress. Flanking this core are dynamic terminal regions, each with a 6,379-base-pair inverted terminal repeat (ITR) that includes an ~80-base-pair hairpin loop, short tandem repeats (70 or 54 base pairs), and unique sequences termed NR1 and NR2. Overall, the genome encodes around 190 open reading frames (ORFs), four of which sit within the ITRs (Chen et al., 2025). Central genes remain highly stable, driving essential viral lifecycle steps, while terminal ones promote virulence and host adaptation—often by blocking antigen presentation, immune detection, signaling cascades, and programmed cell death. MPXV's double-stranded DNA and the proofreading function of its polymerase yield a generally low mutation rate (Chakraborty et al., 2025). Yet, sequencing from the 2022 worldwide outbreak uncovered ~50 extra single-nucleotide polymorphisms (SNPs) versus 2018–2019 strains, hinting at rapid evolutionary shifts. These changes predominantly followed a GA→AA and TC→TT pattern, linked to host APOBEC3 cytidine

deaminase activity (Borges et al., 2023). Phylogenetic studies identified 46 new mutations in 2022 lineages compared to 2018 ones, with 24 non-synonymous alterations potentially reshaping proteins (Yu et al., 2023). Such shifts might explain the outbreak's heightened transmissibility alongside lower mortality, though more studies are needed to clarify their roles in immune escape or overall viral adaptability.

5.0 Diagnosis and Treatment:

Recent progress in molecular diagnostics has introduced high-throughput tests for MPXV, boosting detection speed and capacity. Whole-genome sequencing (WGS) played a pivotal role in the 2022–2023 outbreaks, enabling strain profiling and evolutionary tracking (Misu et al., 2026). Beyond sequencing, DNA-based methods like loop-mediated isothermal amplification (LAMP), restriction fragment length polymorphism (RFLP), and recombinase polymerase amplification (RPA) offer quick, sensitive, and affordable options compared to standard PCR—ideal for low-resource areas (Wang et al., 2024). Serological tools such as enzyme-linked immunosorbent assay (ELISA), Western blot (WB), and immunohistochemistry (IHC) also aid detection when viral samples are scarce. ELISA, the go-to serology test, identifies IgM (emerging soon after rash, peaking in two weeks, fading within a year) and IgG (rising by six weeks, lasting years) (Chauhan et al., 2023). Yet, antibody cross-reactivity with other orthopoxviruses can reduce assay precision. Electron microscopy (EM) confirms infection by imaging MPXV's signature brick-shaped particles but sees limited routine use due to expense and expertise needs (Silva et al., 2023).

Antiviral treatment targets severe cases or at-risk groups, like the immunocompromised, children, pregnant/breastfeeding individuals, or those with skin conditions or multi-organ issues (Pipitò et al., 2025). Figure 2 provides an overview of the characteristic clinical manifestations associated with monkeypox virus infection. It's also recommended for atypical infections in eyes, mouth, genitals, or anus that risk complications. Supportive care—easing symptoms and curbing secondary infections—suffices for most. While no MPXV-specific drugs exist, smallpox antivirals like brincidofovir, tecovirimat, and cidofovir show promise owing to viral similarities. Cidofovir and brincidofovir block viral DNA polymerase to halt genome replication. Tecovirimat, meanwhile, disrupts the VP37 envelope protein, preventing Golgi membrane wrapping of mature virions into extracellular forms (EVs) and curbing host spread (Bruno & Buccoliero., 2023). These diagnostic and treatment innovations have sharpened outbreak responses, improving detection, management, and survival rates.

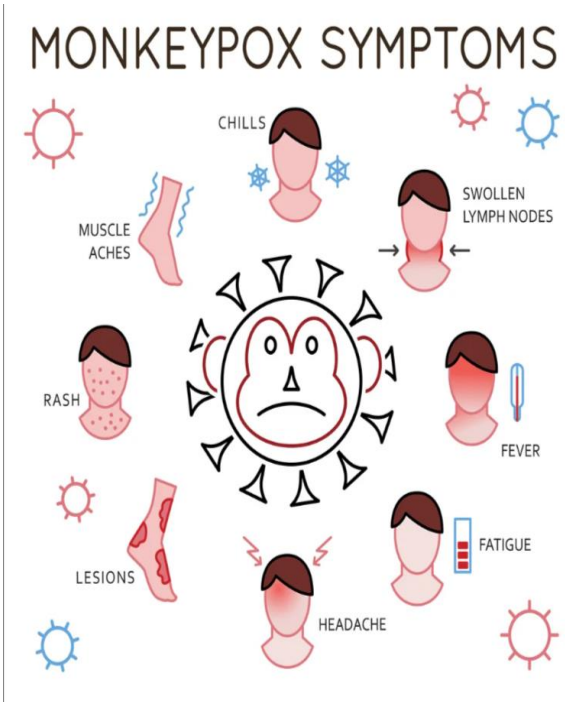

Figure 2: *Symptoms of monkeypox virus*.

6.0 Prevention and Control Strategies:

Curbing monkeypox demands a comprehensive public health strategy that blends surveillance, vaccination, community outreach, and infection control protocols (https://www.cdc.gov/monkeypox/php/public-health-strategy/index.html). As a zoonotic agent, MPXV jumps from animals—especially rodents and non-human primates—to humans, so limiting such interfaces is key to averting spillovers and outbreaks (Fauziah et al., 2024). Tight rules on importing, handling, and moving wild animals further block interspecies jumps and viral entry into people. Outbreak management hinges on swift case identification, patient isolation, and thorough contact tracing to break transmission cycles (Deiana et al., 2026). Rigorous hygiene—like frequent handwashing—and PPE use by healthcare staff are vital to stem human-to-human spread in hospitals and communities.

Sunchatawirul et al. (2026) have proposed an integrated genomic surveillance framework that combines epidemiological, clinical, and genomic data using bioinformatics tools and global data-sharing platforms, aligned with WHO genomic surveillance strategies and International Health Regulations. The framework enhances the early detection of emerging MPOXV variants, supports real-time monitoring of pathogen evolution, and strengthens outbreak response. Overall, it highlights the importance of scalable genomic infrastructure and coordinated data-sharing systems to improve public health preparedness with effective prevention and control strategies.

Vaccines form a cornerstone of defence (Garcia-Atutxa et al., 2024). Smallpox shots cross-protect against MPXV due to genetic overlap, with the third-generation Modified Vaccinia Ankara (MVA-BN, or JYNNEOS/Imvanex) proving highly effective for at-risk groups such as clinicians, lab workers, and case contacts (Pischel et al., 2024). Education campaigns empower communities by highlighting spread pathways, protective habits, and the need for early care. Bolstering lab diagnostics and genomic monitoring tracks changes in transmissibility, severity, or vaccine escape. A "One Health" framework—linking human, animal, and environmental factors—offers the best path to lasting prevention and control.

7.0 Global Health Significance and Future Perspectives:

Monkeypox has emerged as a major global health concern, standing alongside COVID-19 and polio as one of the World Health Organization's three ongoing international health emergencies (https://www.cdc.gov/mpox/situation-summary/index.html). Previously confined mainly to regions of Central and West Africa, monkeypox virus (MPXV) has now spread across continents, with more than 56,000 reported cases worldwide by September 2022, marking the largest outbreak recorded to date (WHO, 2022). This rapid global spread has been driven by environmental and socio-political factors such as climate change, deforestation, population displacement, and armed conflicts, including the Russia–Ukraine war, which increase human–animal interactions and raise the risk of zoonotic disease transmission.

A significant factor contributing to the resurgence of monkeypox is the discontinuation of routine smallpox vaccination following the global eradication of smallpox in 1980. Since smallpox vaccines also provided cross-protection against other orthopoxviruses, the absence of widespread immunization has resulted in reduced population immunity to MPXV. Although universal vaccination is not currently practical, focused strategies such as post-exposure vaccination, antiviral therapy, isolation of infected individuals, and contact tracing have proven effective in limiting transmission. The 2022 outbreak disproportionately affected men who have sex with men (MSM), with many cases presenting unusual genital and perianal lesions, suggesting a role for close physical or sexual contact in virus spread (McQuiston et al., 2023). Similar transmission patterns were observed during Nigeria's 2017 outbreak (Ndembi et al., 2024). MSM populations also experience higher rates of coexisting sexually transmitted infections, including HIV, which may influence disease progression (Ortiz-Saavedra et al., 2023; Montaño et al., 2026). Evidence from Nigeria indicated more severe and prolonged illness in HIV-positive individuals (de Sousa et al., 2022), while studies from Spain reported no significant difference in disease severity. These contrasting findings highlight the need for further research on antiviral effectiveness in co-infected patients. Addressing stigma, discrimination, and homophobia is equally critical, as these barriers discourage timely testing, treatment, and public health engagement within vulnerable communities.

Ongoing outbreak preparedness includes the development of next-generation vaccines (Mayer et al., 2024). Moderna is advancing an mRNA-based vaccine,

while Tonix Pharmaceuticals has developed TNX-801, a live horsepox virus vaccine that has demonstrated promising immune responses and safety in preclinical studies against both smallpox and monkeypox (Trefry et al., 2024). In addition, the MPXV E8L protein—essential for viral attachment to host cells—has been identified as a potential target for future vaccine design (Ahuja et al., 2025). A deeper understanding of viral pathogenesis and host immune responses will be crucial for improving vaccine efficacy and antiviral therapies (Navarro et al., 2024). The strain placed on global healthcare systems by the COVID-19 pandemic has further complicated monkeypox response efforts. As a declared Public Health Emergency of International Concern (PHEIC), monkeypox requires strengthened surveillance systems, rapid diagnostics, public awareness campaigns, and preventive measures (Lamptey, 2023). Training healthcare professionals, ensuring stigma-free healthcare services, and providing equitable vaccine access, particularly for high-risk populations such as MSM, are essential. International collaboration, transparent data sharing, and coordinated research efforts will be key to controlling future MPXV outbreaks and enhancing preparedness for emerging infectious diseases.

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Author Declaration Statements

Declaration: The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript.

Conflict of Interest: All authors confirm that:

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- All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged. **– ~~Yes~~ / Not Applicable**√
- Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable. **– ~~Yes~~ / Not Applicable**√

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